SUMMARY MINUTES

OF THE

HEMATOLOGY AND PATHOLOGY DEVICES PANEL MEETING

OPEN SESSION

January 20, 1999

Gaithersburg Holiday Inn
#2 Montgomery Village Avenue
Gaithersburg, Maryland

Hematology and Pathology Devices Panel

January 20, 1999

Chair

Diane D. Davey, M.D.

Executive Secretary

Veronica J. Calvin, M.A.

Voting Member

Yao-Shi Fu, M.D.

Temporary Voting Members

Mahnaz Badamchian, Ph.D.

Brian S. Bull, M.D.

John Koepke, M.D.

Diane Norback, M.D., Ph.D.

Jerome Nosanchuk, M.D.

Stephen Peiper, M.D.

Consumer Representative

Ellen Rosenthal, M.S.

Industry Representative

Alton D. Floyd, Ph.D.

JANUARY 20, 1999--OPEN PUBLIC SESSION

Panel Chair Diane D. Davey, M.D., called the session to order at 9:12 a.m. Panel Executive Secretary Veronica J. Calvin, M.A., read a brief summary of the last Hematology and Pathology Panel meeting, held on September 4, 1998, at which the panel voted in favor of recommending for FDA approval with conditions the anti-HER2 IHC assay system manufactured by DAKO Corporation. The device received final FDA approval on September 25, 1998. Ms. Calvin outlined the day's agenda, thanked Dr. Davey for chairing the session in lieu of regular Panel Chair Dr. Timothy J. O'Leary, and asked the rest of the panel to introduce themselves. She also read the conflict of interest statement, noting that potential or perceived conflicts had been considered regarding Drs. Koepke and Bull, but their full participation was allowed. Ms. Calvin then read appointments to temporary voting status for Drs. Badamchian, Bull, Koepke, Norback, Nosanchuk, and Peiper for the January 20 session.

Open Public Hearing

Panel Chair Dr. Diane Davey invited public attendees to address the panel. There were no requests to speak.

Sponsor Presentation

Onno W. Van Assendelft, M.D., Ph.D., of the Science Resources Program at the National Center for Infectious Diseases, introduced the day's topic, a petition for reclassification of automated differential cell counters. He summarized the regulatory history of automated differential cell counting devices, beginning with the classification of automated white cell differential counters as Class III devices in the 1970s because of

insufficient information for establishing a performance standard to assess safety and effectiveness. He noted that the 1981 NCCLS proposed standard for leukocyte differential counting led to the reclassification to Class II of automated white cell differential counters used for identification and enumeration of the five white cell types normally present in peripheral blood and argued that subsequent advancements in technology suggest reclassification of automated differential cell counters (ADCCs) remaining in Class III to Class II. The International Society for Laboratory Hematology (ISHL) appointed a task force to prepare a reclassification petition for ADCCs; this task force included members from the medical devices manufacturing industry and laboratory or clinical health care providers, many of whom also represent standards organizations.

Dr. Van Assendelft summarized the three reasons for Class III classification and stated that the ISHL task force believes sufficient information and special controls exist to allow reclassification into Class II. The reclassification petition presented by ISHL summarizes scientific data, references to the published literature, the reasons why the task force recommends Class II for ADCCs, and an analysis of the Medical Device Reports on ADCCs from 1985 until 1997. The petition requests that the FDA reclassify ADCCs that count or classify abnormal or immature cells of the blood or formed elements of the peripheral blood, bone marrow and body fluids from Class III to Class II.

FDA Presentation

Larry J. Brindza. M.P.A., a scientific reviewer from the Immunology, Hematology, and Pathology Branch, presented the chronology of ADCC regulation from 1979 until the present. He listed three FDA concerns about the proposed special control or guidance document. These concerns involved the need for a special control for

hematopoietic progenitor cells, the sufficiency of information in the proposed Reviewer Guidance document to cover matrices other than blood, and the specificity of information to include bands, blasts, immature granulocytes, atypical lymphocytes, nucleated red blood cells, immature reticulocyte fraction, and hematopoietic progenitor cells.

Open Committee Discussion

Panel discussion focused first on the FDA concern about use of matrices other than blood. It was suggested that if manufacturers propose using other fluids, sponsors would need to specify the matrix and provide data to show that cells could be counted and identified. Manufacturers would have to choose the parameters they intend to demonstrate and prove the clinical utility.

The panel also discussed whether hematopoietic progenitor cells should be included in the reclassification petition language, given the lack of a gold standard for what these cells are. Data were presented by Dr. Berend van Houwen on the use of CD34 as a standard for stem cell identification, although it was noted that the technology lacks specificity. He discussed the development of technology intended for detecting the right time for stem cell harvest for autologous transplants. Dr. Gutman of the FDA asked the panel to consider whether this technology is well enough known that general and special controls are sufficient or whether it should be under premarket approval application (PMA) control. He noted that the difference between a high-end 510 (k) and a PMA is blurred and that the FDA can ask for technical data sets as necessary.

Returning to discussion of the second FDA concern on matrices other than blood, the panel was concerned to narrow the discussion to include hematopoietic progenitor cells. The sponsor clarified their intent to limit it to blood cells in any stage wherever

they are found, including hematopoietic cells. It was suggested that the original definition on p. 2 in the proposed Reviewer Guidance document, included in the petition amendment, be revised to say "immature cells in blood, bone marrow, or spinal fluids."

On the third FDA concern, it was noted that the petition specifies that bands not be enumerated. It was suggested that immature granulocytes be defined in the special control and that bands be left out. Blasts and atypical lymphocytes need some labeling requirement in special controls to suggest some initial manual visual verification before labs send out the results—a prereporting checkpoint. Immature reticulocytes are a valuable measurement and ranges could be recommended as part of special controls. Various options on hematopoietic progenitor cells were discussed, including removing the category, keeping them as Class III for use under certain conditions, or developing a guidance document before downclassification is allowed. **Alton Floyd, the Industry Representative on the panel,** noted the lack of a gold standard, especially regarding hematopoietic progenitor cells, and asked whether downclassification and/or cooperation between the FDA and standards bodies to develop special guidance documents is the best solution. It was noted that the NCCLS is working on flagging certain types of cells and could provide information to the FDA. Panel members suggested keeping the guidance document as broad and general as possible and having manufacturers and standards bodies work together on standards development.

Industry Response

Dr. Van Assendelft noted that the reviewer guidance for 510 (k) applications for ADCCs is not meant to be specific to specific cell types but generic. The ISHL task

force's concern was accuracy, and he noted that there are documents available to guide the reviewer on what to look for regarding principles on accuracy and precision claims.

Panel Vote and Recommendations

Marjorie Shulman of the FDA guided the panel through the classification questionnaire. The automated differential cell counters were recommended for reclassification when the device is intended to count or classify immature or abnormal hematopoietic cells of the blood, bone marrow, or other body fluids. The panel decided the device was potentially hazardous to life. The panel thought there was not sufficient information to determine general controls but there was sufficient information to establish special controls. These included testing guidelines (guidance) and labeling as specified on the supplemental data sheet. The device was restricted for prescription use.

On the supplemental data sheet, the panel stated that the device is not an implant. Under indications for use, the panel specified a higher level of review for some claims, saying that where alternative methods exist for verification of the count or classification of the immature or abnormal hematopoietic cells, data as to agreement with these methods must be presented with the request for in vitro diagnostic status. Examples include blast and atypical lymphocyte verification and bone marrow differential counts. Where such methods do not exist, the sponsor must provide an alternative acceptable to the FDA. Examples include progenitor cells. Recommended labeling includes manual verification of blasts and atypical lymphocytes the first time they are flagged. The panel identified misdiagnosis or treatment error as a risk to health presented by the device, specifically by incorrect identification of hematopoietic cells. The advisory panel recommended Class II with high priority on the basis that additional information is now

available, including widespread laboratory experience, published references, and voluntary guidance documents from international or national groups. The device was restricted for prescription use. Existing standards applicable to the device include voluntary guidelines from NCCLS and other groups.

The panel voted unanimously to recommend reclassification of the device to Class II with the restrictions listed in item 4, as noted on the sheets described above.

Executive Secretary Veronica Calvin thanked the petition sponsor, FDA staff, and Panel Chair Dr. Davey. She expressed particular gratitude to Drs. Davey and Fu, whose four-year terms are ending this February. The meeting was adjourned at 2:05 p.m.

I certify that I attended the Open Session of the Hematology and Pathology Devices Panel on January 20, 1999, and that this summary accurately reflects what transpired.

Veronica J. Calvin
Executive Secretary

I approve the minutes of this meeting as recorded in this summary.

Diane D. Davey, M.D.
Acting Panel Chair